1634

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of inventor Saraf

Serial No. 09/870,986 Group Art Unit: 1634

Filed: 06/01/2001 Examiner: Chakrabarti

For: ***"BIO-CHIP TO SEQUENCE UNTAGGED DNA"***

Assistant Commissioner for Patents

Washington, D.C. 20231

REQUEST FOR RECONSIDERATION

Dear Sir:

In response to the Office Action mailed on 09/17/2002, Applicant respectfully requests reconsideration of the above-referenced patent application in light of the following:

REMARKS

The application includes claims 1-23, which represent Applicant's previous election, without traverse, of the "Group I" claims.

35 U.S.C. § 102(e)

Claims 1-23 stand rejected under 35 U.S.C. § 102(e) as anticipated by Caldwell et al., US Patent 6,284,503 B1 (Sept. 4, 2001).

The Office Action states that Caldwell et al., teach a "*tagging-free* method to detect the binding of an *untagged* single stranded nucleic acid sequence to an *untagged* material of interest" (emphasis added). The four steps of the present invention are then outlined and equated to the method taught by Caldwell et al. as follows: a) providing a sensor comprised of a first layer and a second layer, wherein the first layer comprises an untagged single stranded nucleic acid sequence

sequence and wherein the second layer comprises a photo luminescent material, and wherein the first and the second layer are separate layers; b) exposing the sensor to a biological sample for sufficient time for the untagged single stranded nucleic acid sequence to bind an untagged material of interest in the biological sample; c) applying light to the sensor; and d) measuring the photo luminescence from the sensor, wherein photo luminescence measured in the step of exposing is indicative of binding the untagged single stranded nucleic acid sequence to the untagged material of interest. Column 17, lines 55-67 in Caldwell et al. are referenced as the source of this purportedly anticipatory method.

Applicant respectfully submits that the reading and interpretation of Caldwell et al., and the attempt to equate the steps of the method of the present invention with the method described by Caldwell et al., is flawed.

In fact, what Caldwell et al. describes is a PCR technique that employs electrochemiluminescent (ECL) labels for detection of the molecule of interest, in this case, a PCR product.

The dsDNA PCR product is generated using oligonucleotide primers, one of which is linked to a biotin moiety (column 17, lines 55-57). This results in the production of a dsDNA PCR product in which one strand bears a biotin moiety. In order to carry out detection of the PCR product, the dsDNA product is denatured and the ssDNA which bears the biotin moiety is hybridized to "an *ECL-labeled* DNA probe which is complementary to the amplified biotinylated strand" (column 17, lines 58-60). An "ECL label" is an "electrochemiluminescent label". Thus, a hybrid biotinylated-ECL-labeled ds oligo is formed (column 17, line 61), and see diagram 1 in Exhibit A.

The hybrid dsDNA is then exposed to streptavidin coated magnetic beads. In this reaction, the hybrid oligo will bind to the magnetic beads via a binding interaction between the streptavidin on the beads and the biotin moiety on the hybrid oligo. The hybrid oligo will then be tethered on the beads, allowing the removal of unhybridized material by washing the beads. (column 17, lines 62-65).

Finally, "the ECL complexes [i.e. the hybrid attached to the magnetic beads] are excited by chemical, photometric, or electrical means..." (column 17, lines 65-66); and "...the photon

emission measured." (column 17, line 67). Applicant notes that the photon emission that is measured originates from the ECL label that is attached to the dsDNA hybrid oligonucleotide.

In contrast, the present method detects binding of an untagged (i.e. unlabeled) molecule of interest to a ssDNA as follows: the sample which may contain the molecule of interest (which might be, for example, an untagged, denatured- and therefore ssDNA- PCR product) is exposed to a sensor. The sensor is made up of two layers: one layer includes an untagged single stranded nucleic acid sequence and the second layer is made of photoluminescent material. The first and second layers are separate layers. The sample is exposed to the sensor for sufficient time to allow any homologous untagged material of interest in the sample to bind (i.e. hybridize) to the untagged single stranded nucleic acid in the first layer of the sensor. In order to detect whether such a binding event has or has not occurred, light is applied to the sensor; and the resulting photoluminescence is measured. Unlike the method of Caldwell et al., the photoluminescence that is measured does not originate from a tag such as an ECL tag. Rather, the photoluminescence originates from the second layer which is photoluminescent. What is detected in the practice of the present invention is NOT the presence of photoluminescence, which would be indicative of the presence of an extrinsic label. Instead, a change in the photoluminescence of the second layer is measured. A change in the photoluminescence of the second layer will occur if the untagged ssDNA in the first layer has been converted to dsDNA by the binding of a complementary untagged ssDNA from the sample. Neither the ss nucleic acid of the first layer nor the ss nucleic acid of the sample bears a labeling or "tagging" moiety. Thus, in contrast to Caldwell et al., in the present invention, the photoluminescence that is measured thus does not originate from an extrinsic label. The change in the DNA from the single stranded to the double stranded state is enough to cause a change in photo luminescence of the second underlying layer. A thorough, detailed explanation of how this occurs is given in the present application on page 12 at lines 11-33.

To reiterate, as is stated in the first sentence of the Summary of the present application (page 3) "It therefore is an object of this invention to provide methods and products for detecting the hybridization state of a nucleic acid molecule, without needing to tag the sample." Applicant respectfully submits that the method taught by Caldwell et al. is one of those which the present

invention improves upon by eliminating the step of attaching a label to a molecule that one desires to detect, and by providing a detected molecule free of extraneous tags or labels. Applicant notes that the hybrid DNA molecules detected by the method of Caldwell et al. are encumbered with both a biotin moiety on one strand and an ECL label on the other. Use of the method of the present invention in a similar situation would result in the capture on the sensor of an unlabeled complementary DNA strand which could be released from the sensor in its native state and used for other purposes.

In view of this analysis, Applicant respectfully requests reconsideration and withdrawal of this rejection.

35 U.S.C. §103(a) rejection (Examiner's point # 5)

Claims 3, 8-12, 18 and 21-23 stand rejected under U.S.C. 35 §103(a) over Caldwell et al. (US Patent 6,284,503 B1) in view of Bhargava et al. (US Patent 6,241,819 B1). Examiner states that Caldwell et al. teach a method of claims 1, 2, 4-7, 13-17, 19 and 20 as described in the section pertaining to the 102(e) rejection.

The Office Action states that Caldwell et al. do not teach: doped or undoped zinc sulfide in a nanocomposite; the use of ultraviolet light in the range of 200-700 nm; or a first layer positioned on a first side of a second layer, the second side opposite the first side on the second layer, and measuring photoluminescence reflected from the first and second side of the second layer. However, the Office Action states that Bhargava et al. supply these elements and that a combination of Caldwell et al. and Bhargava et al. thus render the present invention obvious.

Applicant respectfully disagrees for the reasons set forth in the previous section regarding Caldwell et al. Briefly, Caldwell et al. describe a method in which detection of the molecule of interest (a PCR amplification product) is carried out by detecting an ECL label which is attached to one of the two strands of the dsDNA. The other strand also has an attached biotin moiety, i.e. both strands of the dsDNA are modified in some manner. In contrast, the method of the present invention (as recited in claim 1) is directed to detection of the binding of a molecule of interest that is not labeled (i.e. is "untagged") to a ssDNA molecule that is also untagged.

Bhargava et al. teach doped semiconductor particles with high luminescent efficiency.

However, Bhargava et al. neither show, allude to, or suggest the desirability or advantages of any type of detection device. In particular, they do not refer to a method such as that of the present invention: a tagging-free method to detect the binding of an untagged single stranded nucleic acid sequence to an untagged material of interest.

In sum, since Caldwell et al. does not show or suggest a tagging-free method for detecting the binding of an untagged single stranded nucleic acid sequence to an untagged material of interest as is required in claim 1 of the present invention, and Bhargava et al. also does not show or suggest such a method, a combination of the two references cannot render the present invention obvious.

In view of the foregoing, reconsideration and withdrawal of this rejection are respectfully requested.

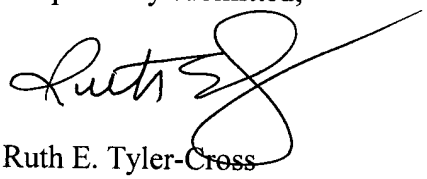
Formal Matters and Conclusion

In view of the foregoing, Applicant submits that all rejections have been successfully traversed. The Examiner is respectfully requested to pass the above application to issue at the earliest possible time.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at the local telephone number listed below to discuss any other changes deemed necessary in a telephonic or personal interview.

Please charge any underpayment or credit any overpayment of fees to attorney's deposit account #50-2041.

Respectfully submitted,



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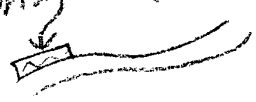
PATENT TRADEMARK OFFICE

Exhibit A

09/870,986

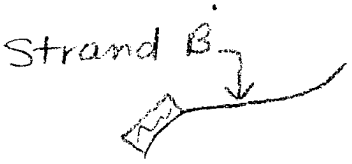
PCR Amplification of oligos, one of which is linked to biotin

= biotin linked primer

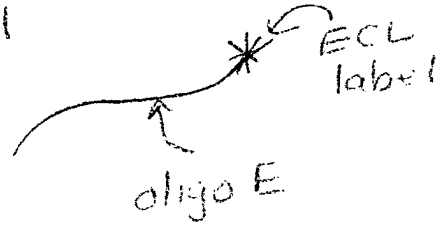


= ds DNA PCR product, one strand ("strand B") linked to biotin

↓ denature

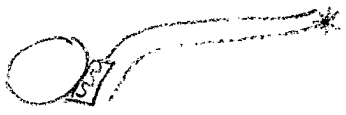


↓ renature with "oligo E", complementary to "strand B" and labeled with an ECL label



= ds DNA hybrid 1) biotin and 2) ECL label

attach to magnetic beads via biotin



wash, detect photoluminescence from ECL label